Association Between Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Early Life and Recurrent Wheeze and Asthma in Later Childhood

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SUPPLEMENT ARTICLES

Association Between Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Early Life and Recurrent Wheeze and Asthma in Later Childhood

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Background. Recurrent wheeze and asthma in childhood are commons causes of chronic respiratory morbidity globally. We aimed to explore the association between respiratory syncytial virus (RSV) infection in early life and subsequent respiratory sequelae up to age 12 years.

Methods. We estimated the strength of association by 3 control groups and 3 follow-up age groups, with data from studies published between January 1995 and May 2018. We also estimated associations by diagnostic criteria, age at infection, and high-risk population.

Results. Overall, we included 41 studies. A statistically significant association was observed between early life RSV infection and subsequent childhood recurrent wheeze, in comparison to those who were healthy or those without respiratory symptoms: OR 3.05 (95% confidence interval [CI], 2.50–3.71) for 0 to <36 months follow-up age; OR 2.60 (95% CI, 1.67–4.04) for 36–72 months; and OR 2.14 (95% CI, 1.33–3.45) for 73–144 months. For the subsequent development of asthma, a statistically significant association was observed only in relation to those aged 73–144 months at follow-up: OR 2.95 (95% CI, 1.96–4.46).

Conclusions. Further studies using standardized definitions and from diverse settings are needed to elucidate the role of confounders and provide more robust estimates.

Keywords. respiratory syncytial virus; recurrent wheeze; asthma; children.

Respiratory syncytial virus (RSV)-associated acute lower respiratory infection (ALRI) is a major cause of hospital admissions in young children, resulting in a substantial burden on health care services. About 45% of hospitalization and in-hospital deaths due to RSV-ALRI occur in children during the first 6 months of life [1]. The development of a safe and effective vaccine to protect young children against RSV infection could have a substantial effect on disease burden in this age group. A monoclonal antibody is available for RSV prophylaxis for at-risk infants; a novel monoclonal antibody and pediatric and maternal candidate vaccines are in the late stages of development [2]. These prophylaxis or vaccination strategies may protect the infants against acute RSV illness during their first months of life. Meanwhile, early childhood RSV-ALRI has been reported to have an association with subsequent development of wheeze-associated disorders in childhood [3, 4]. Recurrent wheeze and asthma in childhood are a common cause of morbidity globally, that lead to decreased quality of life, frequent health care utilization with high health economic costs, and financial burden to families [5, 6]. Whilst some recurrent wheezing may resolve spontaneously, others persist into adulthood. The public health and economic value of RSV prophylaxis and vaccines would be greater if they also decreased the prevalence and severity of wheeze-associated disorders.

The aim of this review is to explore whether there is an association between RSV infection in early life and subsequent respiratory sequelae (recurrent wheeze or asthma) up to age 12 years.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review across 9 databases (including 3 Chinese databases) following the approach detailed in the PRISMA guidelines [7]. Tailored search strategies were developed and applied to search Medline, Embase, Global Health, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Global Index Medicus, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP

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databases (Supplementary Material Strategy). All searches were limited to between January 1995 and May 2018. No publication status criteria or language restrictions were applied. We included studies that fulfilled the selection criteria described in Supplementary Panel 1.

Three investigators (T. S., Y. O., and E. M. Z.) conducted independent literature searches and extracted data using standardized data extraction templates. One investigator (T. S.) whose first language is Chinese performed the search and data extraction from Chinese language databases (CNKI, Wanfang, and Chongqing VIP). Any uncertainties regarding relevance or inclusion were discussed with and adjudicated by T. S.

The protocol of this review was published in the PROSPERO database (No. CRD42018095112).

Definitions

The population under investigation consists of children up to 12 years old because the literature suggests that lung function is lost early in life and this age cutoff should allow exploration of the association with early life respiratory virus infection [8]. This statement assumes that respiratory morbidity varies by age from infancy to adolescence and the impact of early life RSV infection appears to diminish in later childhood. The exposure group was defined as RSV infection with laboratory confirmation in the first year of life (including those younger than 2/3 years). The control group was defined as infants without respiratory symptoms (RSV/noRS); or respiratory infection associated with other pathogens including rhinovirus (RSV/other); or only rhinovirus infection (RSV/RV) (Supplementary Panel 2). Outcomes were recurrent wheeze and asthma. The follow-up age group (up to 12 years old) were categorized into 3 subgroups (0 to <36 months, 36–72 months, and 73–144 months) in order to evaluate the association by age.

Statistical Analysis

We standardized the results of all the included studies as odds ratios (ORs) of detecting the occurrence of the outcome in infants with RSV infection compared to the control group with accompanying 95% confidence intervals (95% CIs) to facilitate interpretation and comparison. We applied a continuity correction of 0.0005 if the outcome was detected in 1 group but not the other [9]. This allowed calculation of an OR for these instances and enabled inclusion in subsequent metaanalyses. Furthermore, adjusted odds ratios (aORs) were also extracted, where possible. These were used preferentially in subsequent calculations and analyses.

Using STATA (version 13.0), we performed a metaanalysis of outcome-specific ORs and reported pooled estimates with corresponding 95% CIs using the random effects model (DerSimonian-Laird method) because the included studies are heterogeneous in various aspects and thus are assumed to have different effect sizes [10]. Each outcome was assessed separately in comparison to 3 control groups. This led to 6 groups of results in total. Within each group, the result was reported as per the above predefined age subgroups. Subgroup analysis stratified by outcome diagnosis (physician diagnosed or parent reported) and age at RSV infection (0–11 months and 0–23 months) were carried out to explore the effect of possible confounders. Similarly, sensitivity analyses in high-risk populations (those with prematurity or atopy) were also conducted.

Quality Assessment

Quality assessment at the individual study level was carried out using the adapted Downs and Black checklist [11]. Items that were not applicable (adverse effects, blinding of subjects, compliance, randomization, concealment) were removed. The power criteria have been defined as having score 1 for providing power calculation and 0 if not. This resulted in evaluation of 22 variables with a maximum score of 22. A score of less than 12 (out of 22) was defined as a low-quality study.

RESULTS

We identified 4520 records and only 41 studies, including about 234 000 children, fulfilled our inclusion criteria (Supplementary Figure 1). Although the search was carried out for articles published from 1995, most (37/41) included studies published since 2000. Four studies were conducted within developing countries while 37 were from industrialized countries. One study was from a rural setting, 37 from urban areas, and 3 from a mix of urban and rural areas. There was considerable variation in the design of included studies. Ten studies were from retrospective cohorts while 31 were prospective cohort studies. The majority of RSV cases were identified from inpatients (31 studies) while the remaining recruited cases from outpatients, emergency departments, clinic visits, or community. Twenty-eight studies reported the outcome of recurrent wheeze. Among them, 17 studies used infants without respiratory symptoms or healthy infants as controls, 14 studies reported outcome data for infants with other pathogen-associated respiratory infection, and 3 studies had data on infants with rhinovirus as the control group. Twenty-six studies reported the outcome of asthma. Among them, 12, 16, and 3 studies were available, respectively, reporting data for the 3 control groups. A table describing features of the studies is available in Supplementary Table 1. Supplementary Tables 2–7 summarize the key characteristics and result of each included study under each category (6 categories under the combination of 2 outcomes and 3 control groups). The metaanalyses results for both outcomes are available in Table 1. Forest plots are available in Supplementary Figure 2.

RSV Infection and Recurrent Childhood Wheeze

In the RSV/noRS group there were 10, 7, and 6 studies, respectively, for the 3 follow-up age groups, 0 to <36 months, 36–72 months, and 73–144 months. The pooled metaanalysis ORs were 3.05 (CI, 2.50–3.71), 2.60 (95% CI, 1.67–4.04), and 2.14 (95% CI, 1.33–3.45), respectively. In the RSV/other group there were 7, 7, and 2 studies for the 3 follow-up age groups. The OR metaestimates were 0.79 (95% CI, 0.32–1.95) for 0 to <36 months and 0.81 (95% CI, 0.39–1.71) for 36–72 months, respectively. For the RSV/RV group there were only 3 studies, all of which had follow-up of 36–72 months, which resulted in the OR metaestimate of 0.41 (95% CI, 0.20–0.83).

We observed that the OR metaestimates for physician-diagnosed recurrent wheeze and parent-reported recurrent wheeze in the RSV/noRS group for children aged 0 to <36 months were 3.40 (95% CI, 2.60–4.46) and 2.48 (95% CI, 1.60–3.85), respectively. We also estimated that the OR metaestimates for recurrent wheeze in the RSV/other group stratified by age at RSV infection (0–11 months and 0–23 months) were 2.11 (95% CI, 1.42–3.12) and 0.30 (95% CI, 0.10–0.97), respectively (Supplementary Table 8 reports results for 0–11 months). In the RSV/noRS group (age 0 to <36 months), sensitivity analysis in premature infants indicated an OR metaestimate of 3.20 (95% CI, 1.82–5.61) compared to 3.06 (95% CI, 2.63–3.55) in the full-term infants.

RSV Infection and Asthma

In the RSV/noRS group, there were 2, 2, and 9 studies, respectively, for the 3 follow-up age groups, 0 to <36 months, 36–72 months, and 73–144 months. The OR metaestimate for the follow-up age group of 73–144 months was 2.95 (95% CI, 1.96–4.46). In the RSV/other group there were 2, 7, and 7 studies for the 3 follow-up age groups. The OR metaestimates for the 36–72 months and 73–144 months follow-up age groups were 1.28 (95% CI, 0.84–1.95) and 0.54 (95% CI, 0.28–1.06), respectively. For the RSV/RV group, there were only 3 studies and each study had a different follow-up age group, which precluded any metaanalyses.

Our subgroup analysis stratified by age at RSV infection (0–11 months and 0–23 months) for the follow-up age of 73–144 months demonstrated OR metaestimates of 3.68 (95% CI, 1.92–7.04) and 2.28 (95% CI, 1.44–3.60), respectively, for the RSV/noRS group (Supplementary Table 8). Similarly, the OR metaestimates were 0.52 (95% CI, 0.17–1.63) for age at RSV infection 0–11 months and 0.41 (95% CI, 0.17–1.01) for age 0–23 months, for the RSV/other group. Sensitivity analysis focusing on atopic infants indicated that the OR metaestimate was 1.73 (95% CI, 1.13–2.64) in the RSV/other group for the 36–72 months follow-up age group.

The score from the quality assessment varied from 11 to 19 after taking into consideration 22 items. There were 4 studies with low quality (score <12 out of a maximum score of 22). Excluding these studies did not change the results substantially, perhaps due to the limited number of studies deemed to be of low quality.

DISCUSSION

This is the first systematic review to evaluate and summarize the literature on the association between RSV infection in early life and childhood recurrent wheeze and asthma, stratified by 3 control groups and 3 follow-up age groups. Our aim was to best synthesize evidence on this association taking into consideration a list of confounders as completely as possible. A previous publication combined all studies and outcome measures, making it difficult to translate findings into public health policy making [12]. This review also identified a number of new studies. Our review summarized data from 41 studies. We demonstrated consistent evidence in support of an association

Table 1. Metaanalyses Results for Association Between RSV Infection During Infancy and Childhood Recurrent Wheeze and Asthma, Stratified by Control Group and Follow-up Age

	Recurrent Wheeze		Asthma	
Follow-up Age, mo	No. of Studies	OR (95% CI)	No. of Studies	OR (95% CI)
RSV vs no respiratory symptoms				
<36	10	3.05 (2.50–3.71)	2	…
36–72	7	2.60 (1.67–4.04)	2	…
>72	6	2.14 (1.33–3.45)	9	2.95 (1.96–4.46)
RSV vs other pathogens				
<36	7	0.79 (0.32–1.95)	2	…
36–72	7	0.81 (0.39–1.71)	7	1.28 (0.84–1.95)
>72	2	…	7	0.54 (0.28–1.06)
RSV vs rhinovirus				
<36	0	…	1	…
36–72	3	0.41 (0.20–0.83)	1	…
>72	0	…	1	…

Abbreviations: CI, confidence interval; OR, odds ratio; RSV, respiratory syncytial virus.

between early life RSV infection and subsequent childhood recurrent wheeze in the RSV/noRS group: OR 3.05 (95% CI, 2.50–3.71) for 0 to <36 months follow-up age, OR 2.60 (95% CI, 1.67–4.04) for 36–72 months, and OR 2.14 (95% CI, 1.33–3.45) for 73–144 months. Although the strength of the association decreased with age, it remained statistically significant. A similar statistically significant association was observed for subsequent asthma episodes in the RSV/noRS group: OR 2.95 (95% CI, 1.96–4.46) for 73–144 months follow-up age (data not available in other follow-up age groups). However, the association was not significant for either outcome in the RSV/other group. In the RSV/RV group, the association was negatively significant for recurrent wheeze (OR, 0.41 [95% CI, 0.20–0.83]) and uncertain for asthma due to a limited number of studies, which might indicate that rhinovirus could play a comparable or even more important role in childhood recurrent wheeze.

Several subgroup analyses and sensitivity analyses were available from this study. The association between RSV infection during infancy and childhood recurrent wheeze was slightly higher in the physician-diagnosed strata (OR, 3.40 [95% CI, 2.60–4.46]) compared to parent reported (OR, 2.48 [95% CI, 1.60–3.85]) with overlapping 95% CIs (only data in the RSV/noRS group with 0 to <36 months follow-up age). This might demonstrate the difference in the ability of physicians and parents to accurately diagnose recurrent wheeze. In the high-risk premature cohort population, a slightly stronger association (with overlapping CIs) was observed with recurrent wheeze (RSV/noRS group with 0 to <36 months follow-up age). The definition of prematurity varied across studies from <37 weeks to 32–35 weeks of gestational age. In another high-risk cohort population (atopy), a stronger association was observed with asthma (RSV/other group with 36–72 months follow-up age). Children at high risk of atopy were defined as having at least 1 parent with respiratory allergies and/or a history of physician-diagnosed asthma. All these subgroup analyses and sensitivity analyses were based on a limited number of studies and the results were usually only available under specific subgroups. Consistent and more robust results would require more studies.

Although a thorough search was carried out across 9 databases, including 3 Chinese language databases, only 41 studies from the published literature were identified meeting our eligibility criteria. The number of studies was even smaller when metaanalyses were carried out stratified by outcome, control group, and follow-up age group. Limited studies were available for subgroup or sensitivity analyses to explore the heterogeneity by diagnostic criteria (physician diagnosed or parents reported), age at RSV infection, and high-risk cohort population (prematurity, atopy). Most studies (37/41) were from industrialized countries and from urban areas, thus evaluating the influence of region or setting on the association of interest was not possible. Also, there were insufficient studies to evaluate the impact of severity of RSV infection in early life on the association because RSV cases in most studies (31/41) were identified from inpatients. Similarly, 31 of the 41 studies were prospective cohort studies. Moreover, the sample size in the RSV exposure group varied from 20 to 1266 and from 9 to 138 326 in the control group. The small sample size undoubtedly contributed to the imprecise 95% CIs calculation of some ORs. Therefore, more studies with larger sample sizes are required to produce more robust estimates for the above variables.

Apart from the variables discussed above, there were many other confounders that should be considered in order to evaluate the true association. Only 9 studies recruited a control group matched on date of birth, gender, residence, or ethnicity. Most studies (30/41) reported crude OR without taking into consideration other confounders. The remaining studies (11/41) reported adjusted OR, adjusting for 1 or several of the following: age, gender, prematurity, birth weight, seasonality, duration of breastfeeding, maternal age, maternal education, maternal smoking during pregnancy, maternal history of asthma, ethnicity, care-seeking behavior, day care attendance, or siblings. Coinfection detection was not considered in most studies. For those studies that did consider this, 1 study excluded coinfection while 8 included coinfection. Some studies (24/41) compared the characteristics between exposure group and the control group and others did not. Due to the nature of the study design (retrospective or prospective cohort studies), some participants were lost to follow-up during the study period. Only a few studies (8/41) discussed the characteristics of participants who were lost to follow-up and their possible impact on the result.

The definitions for recurrent wheeze and asthma varied substantially. For recurrent wheeze, ≥3 episodes of wheezing in the last 12 months was a commonly used definition in the majority of studies (13/28). However, ≥1 episode per year (11/28) and any wheeze during the follow-up (4/28) were also used. For asthma, some studies used current medication for asthma, or physician diagnosed asthma, or required symptoms of asthma within last 12 months, while others also accepted asthma diagnosis at any point during follow-up. There was no standardized asthma definition. Only 4 studies utilized the validated International Study of Asthma and Allergies in Childhood questionnaire. Research on respiratory morbidity suffers from a lack of adherence to international definitions. Four studies with a follow-up age group <5 years old also reported asthma outcome; however, this may pose diagnostic difficulty as objective testing such as spirometry is more challenging in young children [13].

Six studies evaluated the association between RSV prophylaxis (palivizumab or motavizumab) in infancy and childhood recurrent wheeze or asthma [14–19]. These were excluded from the analysis as they were designed (usually randomized controlled trials) to answer a slightly different research question that would be more appropriate to assess in a future analysis, in order to provide more complete evidence on the association

between RSV prophylaxis (or vaccine) strategy in early life and childhood respiratory sequelae. Similarly, among these studies, many variations existed: they recruited cases (receiving RSV prophylaxis) and controls (not receiving RSV prophylaxis) from different settings, used different case/control ascertainment, applied different definitions for the controls, investigated different outcomes, used different definitions and diagnosis methods for outcome, and reported varied follow-up age groups. In these studies, the association between RSV prophylaxis during infancy and childhood recurrent wheeze varied from OR 0.25 (95% CI, 0.09–0.72) to 1.10 (95% CI, 0.60–2.00). For asthma, there was only 1 study reporting the association (OR, 0.52 [95% CI, 0.31–0.87]) [19]. More studies to assess the effects of RSV prevention on these childhood respiratory outcomes are required.

The association between RSV infection during infancy and subsequent childhood recurrent wheeze and asthma may not necessarily indicate causation. Other criteria should be taken into consideration first before causality can be concluded. On applying Bradford Hill criteria [20], we observed that the strength of association varied across the control groups and follow-up age groups. The association was not specific but did have a temporal sequence between exposure and outcome. The remaining criteria were uncertain due to either a lack of evidence or there being inconsistent evidence available. However, the absence of these Bradford Hill criteria does not rule out a possible causal relationship. There are many methodological issues that should be taken into consideration to define causality [21]. Therefore, the association between RSV infection during infancy and childhood respiratory sequelae should be interpreted carefully.

There is considerable international attention on RSV infection in young children at this time when novel vaccine and antiviral strategies are being evaluated and prioritized [2, 22] and more accurate estimate on the long-term effect of RSV on childhood recurrent wheeze and asthma would help to plan for maternal RSV vaccines as well as future policies and interventions.

In conclusion, this review provides some evidence supporting an association between RSV infection in early life and childhood recurrent wheeze and asthma. However, this is only when comparing to infants without respiratory symptoms. Further studies using standard definitions are needed to elucidate the surrounding confounders and provide more robust estimates regarding the association between viral respiratory disease in early life and childhood respiratory sequelae.

SUPPLEMENTARY DATA

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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